

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

HEXAZINONE

Chemical Code # 001871, Tolerance # 00396
SB 950 # 086

September 16, 1997
Revised: 8/10/00, 9/6/02

I. DATA GAP STATUS

Combined, rat (Chronic & Onco):	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect.
Oncogenicity, mouse:	No data gap, possible adverse effect.
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, possible adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.
All record numbers through 187331 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T020906
Prepared by M. Silva, 9/16/97; 8/10/00, 9/6/02

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

073, 074, 103 129444, 129464, 175415 "Combined Chronic Toxicity/Oncogenicity Study with INA-3674 (Velpar) Two Year Feeding Study in Rats," (Kaplan, A.M.—primary author; D.E. Malek—Revision #1; MacKenzie, S.A.—Revision #2; Wood, C.K.—Supplement #2; E.I. du Pont de Nemours & Co., Haskell Laboratory for Toxicology and Industrial Medicine, Report #: 353-77; Medical Research Project #: 1833-001, Completed 5/13/77; Revision #1: 12/17/93; Supplement #2: 3/11/94; Rebuttal: 5/25/00—DuPont Report #: 4346). Hexazinone technical (94-95.8% pure) was fed in diet to ChR-CD rats (36/sex/dose) at 0, 200, 1000 or 2500 ppm for 2 years. On day 112 20/sex/dose were removed for a study on reproduction and returned after mating for males and weaning of pups for females. NOEL = 1000 ppm (Body weights were decreased in both sexes at 2500 ppm. There was a small but statistically significant increase in the total leukocyte count and in the relative number of eosinophils in males at 2500 ppm.) NO ADVERSE EFFECT INDICATED. This study is acceptable as an oncogenicity study. The chronic rat data gap can be filled, even though ophthalmology was not performed. Chronic rat data from this study, in combination with the ophthalmology data from the chronic dog study (396-058, 075/115357, 129465) fill the chronic rat data gap. M. Silva, 9/3/97 and 8/8/00.

074 129465. Supplement 129444. Individual clinical observation data, no worksheet. (M. Silva, 9/15/97).

NOTE: 073 129444 is a revised report of 029 & 030 035174 (see CHRONIC TOXICITY, RAT).

CHRONIC TOXICITY, RAT

029 & 030 035174, "Long Term Feeding Study in Rats with Sym-triazine-2,4 (1H, 3H) - Dione,3-cyclohexyl-1-methyl-6-dimethylamino- (INA-3674), (Haskell Laboratory, HL 353-77, 5/13/77). INA-3674 90% W.P., admixed with the feed at concentrations of 0, 200, 1000 or 2500 ppm and fed to 36 ChR-CD rats/sex/group for 2 years. Twenty/sex/group were removed at 112 days to start reproduction study and returned to chronic study after mating for males and after pup weaning for females. Slight body weight effect was present for mid dose females and for high dose males and females. UNACCEPTABLE, perhaps upgradeable (analytical data on diets and clinical observations not presented; no ophthalmology exam; too few animals/group). (D. Shimer, J. Parker, 11/20/85)

006 020170. Same study as 035174 but without tabulated data and appendices.

008 020175. Summary of 035174. A number of toxicological study summaries is submitted with a cover letter dated 3/15/79. A toxicological study summary (20175) is included but without a specific description. However, the treatments and results fit those described in the above chronic/onco study (035174 dated 5/13/77).

037 043784 This document contains diet analysis and individual and summary clinical observations for study 035174. M. Silva, 9/15/97.

CHRONIC TOXICITY, DOG

**** 058, 075 115357, 129465** "Chronic Toxicology Study in Dogs with DPX-A3674-207 (Hexazinone)," (Dalgard, D.W., Hazleton Washington, HWA Study #: 201-956, 11/5/91). Hexazinone (98% pure) was fed in diet to Beagle dogs (5/sex/dose) at 0, 200, 1500 or 6000 ppm for 52 weeks. NOEL = 200 ppm (There was decreased body weight and food consumption and increased clinical effects, some hematology and clinical chemistry in both sexes at ≥ 1500 ppm. There were decreases in absolute and relative weights of heart, kidney and testes, as well as increases in absolute and relative liver and parathyroid/thyroid weight at 6000 ppm, but there were also some significant effects at 1500 ppm. Increased liver (≥ 1500 ppm) and epididymal pathology were observed (6000 ppm.)) **ACCEPTABLE. POSSIBLE ADVERSE EFFECT: Increased liver pathology at ≥ 1500 ppm.** Volume 075 contained ophthalmology data for the chronic toxicology study in dogs. M. Silva,

075 129465. Ophthalmology Data for Chronic Toxicology Studies in Dogs (Hexazinone). Supplement to HLO 164-91.

CHRONIC TOXICITY, HAMSTER

008 020174. "Chronic Oral Toxicity - Hamsters (male and Female, Golden Syrian", (Haskell Laboratory, 1979). Unformulated hexazinone was admixed with the feed at concentrations of 0, 200, 1000, 1500, 2500 and 5000-7500-10000 ppm to golden hamsters for 48 weeks. Test terminated at week 48 due to disease related mortality (not compound related). (J. Remsen, 4/4/85).

ONCOGENICITY, MOUSE

**** 031-032, 076- 078 & 080 035176, 035177, 129466, 129472, 129468 & 129983** "Two-Year Feeding Study in Mice - Velpar Technical (Analysis of Velpar Mouse Diet Samples; Supplement #1; Revision #1 to Supplement #2; Supplement #3)," (Goldenthal, E.I., International Research and Development, HLO 414-81, 6/23/81). Velpar technical (95-99% pure) was fed in diet to CD1 mice (80/sex/dose) at 0, 200, 2500 or 10000 ppm for 104 weeks. Chronic NOEL = 200 ppm (There was an increase in chronic effects on the liver and a decrease in body weight, primarily in males at ≥ 2500 ppm.) Oncogenicity NOEL = 2500 ppm (The chronic effects on the liver could be preneoplastic in both sexes at 2500 ppm (males) and 10000 ppm in females. There was an increase in hepatocellular adenomas and carcinomas in females at 10000 ppm.) **Possible adverse effect.** Previously reviewed as unacceptable (Remsen, 10/11/85), upon submission of the requested data (historical tumor data, analysis of diet and re-evaluation of liver lesions), the study has been upgraded to **ACCEPTABLE**. (M. Silva, 9/11/97)

059 115358. Historical data supplement to 35176 and 35177 (volume 076 129466 is an exact duplicate). M. Silva, 9/15/97.

078 129472. Diet analysis, supplement to 35176 and 35177. (No worksheet, M. Silva, 9/15/97).

077 & 80, **Record #** 129468 & 129983. Supplement to 031 & 032 35176 & 35177. Reevaluation of liver histopathology. "Weak" oncogenicity is indicated for high dose females. No worksheet, M. Silva, 9/15/97.

REPRODUCTION, RAT

****056 112640** "Reproductive and Fertility Effects with IN A3674-207, Multigeneration Reproduction Study in Rats," (Mebus, C.A., E.I. du Pont de Nemours & Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; 9/11/91) Hexazinone technical (98% pure, 100% by analysis) was fed in diet for 2 generations to CrI:CD BR rats (30/sex/dose/generation; 1 litter for F0 & 2 litters for F1) at 0, 200, 2000 or 5000 ppm. **Systemic NOEL = 200 ppm** (There was decreased body weight and body weight gain at 5000 ppm in the F1 generation males during premating. P1 females had decreased body weight and food consumption during premating and decreased body weight during gestation and lactation at 5000 ppm. F1 females at ≥ 2000 ppm had decreased body weights and body weight gains during premating and gestation at ≥ 2000 ppm and during lactation at 5000 ppm. F1 females had decreased food consumption throughout the study at 5000 ppm. P1 and F1 males had increased absolute and relative testes weights at 5000 ppm.) **Reproduction NOEL ≥ 5000 ppm** **Pup NOEL = 200 ppm** (Pup body weights were significantly decreased at ≥ 2000 ppm. There was a significant increase in "small whole body" in the F2B generation (pups and litters) at 5000 ppm.) **No adverse effect. Acceptable.** (M. Silva, 9/9/97).

029 035173, "Long Term Feeding Study in Rats with Sym-triazine-2,4 (1H, 3H)Dione,3-cyclohexyl-1-methyl-6-dimethylamino- (INA-3674), (Haskell Laboratory, HL 353-77, 5/13/77). INA-3674 90% W.P., admixed with the feed at concentrations of 0, 200, 1000 or 2500 ppm and fed to 20 ChR-CD rats/sex/group/generation (1 litter/generation) for 3 generations. Slight body weight decrease was observed for high dose male and female and for mid dose female adults. Marginal body weight decrease is indicated for high dose group. UNACCEPTABLE. Not upgradeable (necropsy on pups not performed; no histology and clinical observation presented). (D. Shimer and J. Parker 11/22/85).

037 043786 This volume contains justification for dose selection, diet analysis and individual and summary animal data for study 035173. M. Silva, 9/15/97.

033 035178. Supplement to 029 035173.

006 020169, Same study in 029 035173, but without tabulated data.

008 020176. Summary of 35173. A number of toxicological study summaries is submitted with a cover letter dated 3/15/79. A reproductive study summary (020176) is included but without a

specific description. However, the treatments and results fit those described in the above reproduction study (035173 dated 5/13/77).

009 020165. Summary of a 90-Day Feeding and One Generation Reproductive Study - Rats. Rats received dietary levels of 0, 200, 1000 and 5000 ppm for ninety days. Maternal body weight gain decreased and weanlings body weight was lower for the high dose group.

UNACCEPTABLE. Insufficient information. (J. Remsen, 4/485).

TERATOLOGY, RAT

** 104 175416 "Teratogenicity Study of INA-3674 in Rats," (Mullin, L.S.; E.I. Du Pont De Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Haskell Laboratory Report #: 748-86; 1/30/87). Hexazinone technical (INA-3674; 99.26% pure) was administered by gavage to mated female Crl:CD[®]BR rats (25/dose) at 0 (vehicle = 0.5% methyl cellulose; 4000 centipoise), 40, 100, 400 and 900 mg/kg/day during days 7 – 16 of gestation. Maternal NOEL = 100 mg/kg/day (A female died at 900 mg/kg. Bodyweight gain was significantly decreased (17-37%) at 900 mg/kg. Food consumption was decreased at \geq 400 mg/kg. Clinical signs (alopecia, stained chin, stained nose and total rats with signs) were increased at 900 mg/kg. Relative liver weights were significantly increased at \geq 400 mg/kg.) Developmental NOEL = 400 mg/kg (Fetal bodyweights were significantly decreased at 900 mg/kg. There was a significant increase in total number of fetuses with malformations and total % of fetuses with variations affected/litter.) No adverse effects. Acceptable. M. Silva, 8/4/00.

011 983111, "Teratogenic Study in Rats with Sym-triazine-2,4 (1H, 3H)Dione,3-cyclohexyl-1-methyl-6-dimethylamino- (INA-3674), (Haskell Laboratory, Rpt. No.: 265-74, 4/9/74). INA-3674 97.5% purity, admixed with the feed at concentrations of 0, 200, 1000 or 5000 ppm and fed to 25-27 pregnant female CD rats/group. High dose showed minimal toxicity (decreased weight gain). UNACCEPTABLE. Not upgradeable (Analysis of dosing solution not done and lack of sufficient data for offspring). (DS and J. Remsen, 4/5/85).

008 020175. Summary of 983111. A number of toxicological study summaries is submitted with a cover letter dated 3/15/79. A teratology study summary (020175) is included but without a specific description. However, the treatments and results fit those described in the above teratology study (983111 dated 4/9/74).

037 043787 This volume contains dose selection information, analysis of hexazinone in diet, and a discussion of missing data for study 983111. M. Silva, 9/15/97.

TERATOLOGY, RABBIT

** 109 187331 "Hexazinone (DPX-A3674) Technical: Developmental Toxicity Study in Rabbits," (Munley, S.M.; E.I. Du Pont De Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Work Request #: 13619; Service Code #: 843; Laboratory

Project ID #: DuPont-7405; 5/3/02). Hexazinone (DPX-A3674) Technical (98.78% pure) was administered by gavage to mated Hra:(NZW)SPF female rabbits (22/dose) at 0 (0.5% aqueous methylcellulose), 20, 50, 125 and 175 mg/kg during gestation days 7 – 28. Maternal NOEL = 50 mg/kg/day (There was a treatment-related increase in animals found dead, killed *in extremis* and that aborted at ≥ 125 mg/kg. Food consumption was statistically significantly decreased throughout gestation at 125 mg/kg. There was a statistically significant increase in clinical observations at ≥ 125 mg/kg (lethargy, no feces on cageboard, sacrificed *in extremis*, weak, stained tail, stained cageboard, abnormal gait or mobility, aborted, alopecia, diarrhea, found dead, hunched over).) Developmental NOEL > 175 mg/kg/day (There was no treatment-related effect on fetuses at any dose.) No adverse effect. Acceptable. M. Silva, 9/5/02

034, 102 035199, 175414 “Teratology Study in Rabbits H-12932 (Final Report)” and “Hexazinone – Response to California Environmental Protection Agency Questions Concerning Rabbit Developmental Toxicity Study (HLO 148-80),” (Cole, S.S., Original Study: Hazleton Laboratories, Vienna, VA; Project #: 201-522; 2/14/80; Shuey, D.L.; Rebuttal: E.I. du Pont de Nemours and Company, Wilmington, DE; 5/25/00). Hexazinone technical (1,3,5-triazine-2,4,(1H,3H)-dione, 3-cyclohexyl-6-(dimethylamino)-1-methyl; 100% pure) was administered by gavage at 0 (0.5% methocel), 20, 50 and 125 mg/kg/day to artificially inseminated New Zealand White female rabbits (17/dose) on days 6 through 19 of gestation. Previously reviewed as not acceptable and not upgradeable (Parker, 10/29/85; only 1/3 of fetuses had a visceral examination & marginal maternal toxicity), upon re-evaluation and consideration of the registrant’s discussion, the study remains unacceptable and not upgradeable for the reasons previously described. M. Silva, 8/9/00.

037 043790 This volume contains a discussion of maternal and developmental toxicity from study 034 035199. M. Silva, 9/15/97

GENE MUTATION

** 035 35181, "Chinese Hamster Ovary Cell Assay for Mutagenicity (1,3,5-triazine-2,4,(1H,3H)-dione, 3-cyclohexyl-6-(dimethylamino)-1-methyl", (Haskell Laboratory, HL 56 01, 3/26/81). Hexazinone, 95% purity, at concentrations of 0, 2.0, 11.1, 13.1, 13.9 and 14.3 mM, with and without metabolic activation, were evaluated for mutagenic potential on Chinese hamster ovary cells (CHO-HGPRT). Exposure time was for 15-19 hours w/o S-9 mix and 5 hours with S-9 mix. In a repeat test, there were no evidence of increased mutation frequency with an approximated 50% survival decrease. ACCEPTABLE. (D. Shimer and Remsen, 10/10/85).

006 983112, "Mutagenic Activity of s-Triazine-2,4(1H,3H)-Dione, 3-Cyclohexyl -6-Dimethylamino -1-Methyl in the Salmonella/Microsome Assay", (Haskell Laboratory, HL 588-77, 7/29/77). INA-3674-112, purity not given, at concentrations of 0, 400, 800, 1000, 1200, 1600 and 2000 ug/plate with and without rat liver activation system (S-9 mix) were evaluated for mutagenic effect on Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100. Exposure time was for 48 hours. The number of revertants did not increase with any of the hexazinone treatments. UNACCEPTABLE. Insufficient information (no dosing solution analysis; no repeat trial; no indication of solubility or toxicity problems at the high dose). (J. Remsen, 4/5/85).

008 020172. Summary of 983112.

035 035180. Duplicate of 983112.

037 043789 This volume contains additional data for study 983112. M. Silva, 9/15/97

CHROMOSOME EFFECTS

** 035, 037 035183, 043788 "In Vivo Bone Marrow Cytogenetic Assay in Rats - H# 14555 (1,3,5-triazine-2,4(1H,3H)-dione, 3-cyclohexyl-6-(dimethylamino)-1-methyl)," (Hazleton Laboratories, 12/9/82). Hexazinone technical (100% pure) was administered by gavage in a single dose at 0, 100, 300 and 1000 mg/kg to Sprague-Dawley CD rats (3/sex/dose). Terminations occurred at 6, 12, 24 and 48 hours. Bone marrow was examined for clastogenic activity. No compound-related aberrations were reported. Previously reviewed as unacceptable (Remsen, 10/11/85), upon submission of additional information, the study is now upgraded to **acceptable**. (M. Silva, 9/15/97).

** **035 035182**, "In Vitro Assay for Chromosome aberrations in Chinese Hamster Ovary (CHO) Cells (1,3,5-triazine-2,4(1H,3H)-dione, 3-cyclohexyl-6-(dimethylamino)-1-methyl)", (Haskell Laboratory, HL 768-82, 12/28/82). Hexazinone, purity 95%, at concentrations of 0.10, 0.32, 3.17, 7.93, 15.85 and 19.82 mM, with and without metabolic activation were evaluated for mutagenic potential on Chinese Hamster (CHO) cells after a 10 or 2 hour exposure time. **Aberrations, weighted lesions/cell and % abnormal cells increases** were evident, especially without metabolic activation. Positive results were also seen in a repeat test. **ACCEPTABLE**. (D. Shimer and Remsen, 10/11/85).

DNA DAMAGE

** 035 035179, "Unscheduled DNA Synthesis/Rat Hepatocytes In Vitro (1,3,5-triazine-2,4(1H,3H)-dione, 3-cyclohexyl-6-(dimethylamino)-1-methyl)", (Haskell Laboratory, HL 766-82, 12/8/82). Hexazinone, purity 95%, at 0 - 30 mM were evaluated for mutagenicity on primary rat (Sprague-Dawley) hepatocytes after an 18 hour (with 3H-thymidine) exposure period. No UDS reported in either the initial and repeat trial. **ACCEPTABLE**. (D. Shimer and Remsen, 10/10/85).

NEUROTOXICITY

Not required at this time.